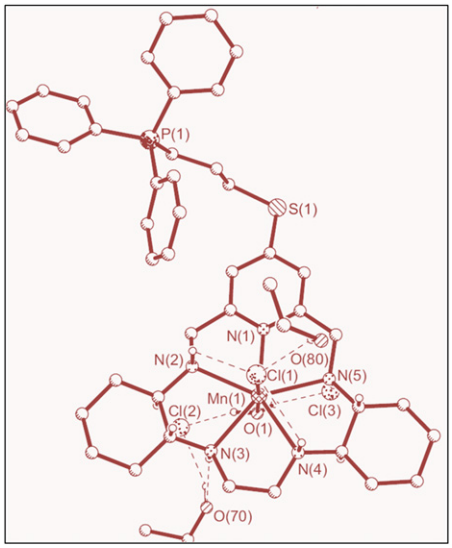
Chemistry & Biology

In This Issue

In Review: AMP-Activated Protein Kinase

PAGE 1222

AMPK is a sensor of cellular energy status activated by metabolic stresses that deplete ATP, and drugs that activate AMPK may be useful for treatment or prevention of type 2 diabetes and cancer. Hardie et al., using diverse examples, review the mechanisms of AMPK activation and implications for drug development.



Superoxide Dismutase Mimetic Enters Mitochondria

PAGE 1237

Kelso et al. develop a mitochondria-targeted superoxide dismutase (SOD) mimetic, MitoSOD, by conjugating a triphenylphosphonium cation to a superoxide-selective pentaaza macrocyclic Mn(II) complex. MitoSOD is the first mitochondria-targeted SOD mimetic that selectively protects mitochondria from superoxide damage.

Big Dig for Adenosine Aptamers

PAGE 1247

Adenosine-binding aptamers represent a paradigm of convergent molecular evolution, although one not previously found in genomic sequences. Vu et al. discover these RNAs in organisms spanning from bacteria to humans and find two new aptamers in a human genomic library, one of which maps to an intron of the *FGD3* gene.

Bacteria Chew Up Cancer Drugs

PAGE 1255

Environmental bacteria are exposed to numerous natural products, which are often exploited as drugs. Westman et al. demonstrate that these bacteria can modify or degrade anticancer drugs, such as doxorubicin, that are shown to be inactivated by deglycosylation, similar to human cardiac tissue during chemotherapy.

The Beauty of E1-E2-E3 Cascades

PAGE 1265

Ubiquitin is transferred to cellular proteins through cross-reacting E1-E2-E3 enzymatic cascades. Zhao et al. engineered specific pairwise interactions between ubiquitin and E1 and E1 and E2 to construct an orthogonal ubiquitin transfer cascade and map the signal transduction networks mediated by ubiquitination.

Taking Apart Bottromycin Biosynthesis

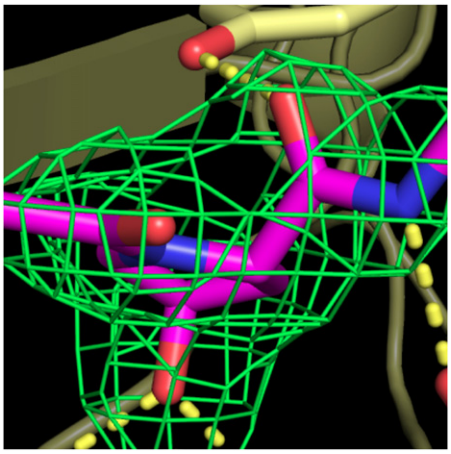
PAGE 1278

Huo et al. describe biosynthetic machinery for bottromycins, a class of antibiotics. Identified genes were introduced into a host to yield optimized producer strains and enable pathway engineering. Bottromycins biosynthesis involves radical SAM methyltransferases and cyclizations via an amidine formation.

Pesky Cystic Fibrosis Mutant Gets a Sponge Bath

PAGE 1288

The most common mutation that causes cystic fibrosis is F508del in CFTR. Trafficking of this misfolded protein can partially restore protein function. Carlile et al. report that a marine natural product, latonduines, corrects F508del-CFTR trafficking by targeting the PARP protein family.



Creating a pVHL:Hif1α Lead Fragment by Fragment

PAGE 1300

Fragment screening is widely used to find novel starting points for drug design, yet its potential and limitations to assess the ligandability of often undruggable protein:protein interactions (PPIs) is underexplored. Van Molle et al. report a rigorous analysis of lead-like inhibitors of the pVHL:Hif1α PPI.

One Assembly Line, Two Polyketide Chains

PAGE 1313

Quartromicins possess a unique symmetrical structure with four spirotetronate units. He et al. show that the tetronate ring intermediates could be reconstructed in vitro and suggest a module-skipping strategy for the production of two alternative polyketide chains by the same polyketide synthase assembly line.

Synthesizing Darwinian Evolution

PAGE 1324

Sczepanski and Joyce construct a synthetic genetic system based on populations of replicating RNA enzymes, implementing a user-specified genetic code to relate genotype and phenotype on a molecule by molecule basis. These molecules were made to compete for limited resources, undergoing Darwinian evolution.

Sensor for Malonyl-CoA

PAGE 1333

Metabolite analysis is largely confined to measurements of whole tissues or cellular populations, neglecting metabolic cross talk between cells. Ellis and Wolfgang generate a mammalian genetically encoded sensor for malonyl-CoA, a critical metabolite for long chain fatty acid synthesis and their β-oxidation.

Tackling Spinocerebellar Ataxia Type 2

PAGE 1340

Kasumu et al. develop a selective positive modulator, NS13001, of calcium-activated potassium channels. NS13001 normalizes electrophysiological properties of cerebellar Purkinje neurons from spinocerebellar ataxia type 2 (SCA2) mouse model and alleviates behavioral and neuropathological phenotypes of aging.

